## REMARKS

Claims 1-16 are pending in the application. For the Examiner's convenience these claims are set forth herein in Appendix A.

Attached hereto is a marked-up version of the changes made to the specification by the current amendments. The attached page is captioned "Version With Markings to Show Changes Made".

*No new matter has been added.* Any amendments to and/or cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

***Declaration of an Interference is the Appropriate Relief in an Inventorship Dispute Before the U.S. Patent and Trademark Office***

Applicant respectfully submits that, based on the facts set forth in the Letter Regarding Rights of Priority Under 35 U.S.C. §119(e) filed on December 15, 2000 and already discussed with the Examiner during the telephonic interview of December 17, 2002, the substance of which is re-iterated herein, it is evident that an inventorship dispute exists between the Applicant of the instant application and the Applicants of U.S. Application Publication Numbers 20020007122A1 and 20020127735A1.

Applicant submits that he is the first to invent the presently claimed subject matter, as evidenced by the plethora of publications made by the Applicant in this field (see, for example, the *Journal of Photochemistry and Photobiology* article submitted by Applicant on November 25, 2002). Applicant's publications prompted the company Medispectra (the employer of Applicants of U.S. Application Publication Numbers 20020007122A1 and 20020127735A1) to contact Applicant seeking more information on the technology. A business relationship ensued and an agreement was reached under which Applicant provided Medispectra with confidential information pertaining to the technology that is the subject of the present application and claims,

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*i.e.*, the detection, staging and mapping of neoplasias, based on the quantitative assessment of acetic acid-tissue interaction kinetics. It is Applicant's belief that based on the foregoing confidential information provided by the Applicant of the instant application, the Applicants of U.S. Application Publication Numbers 20020007122A1 and 20020127735A1 (employed at Medispectra) filed the foregoing published patent applications.

In view of the foregoing, it is evident that there exists a genuine dispute of inventorship and Applicant respectfully submits that the appropriate avenue to resolve this dispute is to have an interference declared between the instant application and U.S. Application Publication Numbers 20020007122A1 and 20020127735A1. As pointed out to the Examiner during the telephonic interview of December 17, 2002, the Examiner in U.S. Application Publication Number 20020007122A1 has, in a first Office Action, indicated claims 18-34 as allowable (see page 6 of the Office Action, submitted herewith as Appendix B). A latest search of the PAIR database indicates that a Notice of Allowance was mailed for this application and that issue revision was completed (see Appendix C). ***Thus, time is of the essence and Applicant respectfully requests that the Examiner indicate the pending claims as allowable and declare an interference, in view of the remarks presented herein.***

***Finally, Applicant respectfully submits that it is unfair to Applicant and contrary to United States Patent and Trademark Office practice and policy to further delay prosecution of the present application, thus allowing the claims in U.S. Application Publication Number 20020007122A1 to issue without an opportunity for an interference to be declared.***

The following remarks are presented herein in support of the patentability of the pending claims.

***Objection to the Drawings***

The Examiner has objected to the drawings filed on December 15, 2000 because, according to the Examiner, "the acronyms 'NAT' and 'NATC' appear to be misplaced." In particular, the Examiner is of the opinion that

> [o]n page 14, lines 8-10 of the specification applicant refers to a "curve" ATC and a "curve" NATC. Figure 1 of the drawings illustrates two straight lines (not curves) that are labeled "NAT" and "NATC". Clarification of this matter is required.

Applicant respectfully submits that the specification has been amended and a substitute Figure 1 is submitted herewith, thereby clarifying the inconsistency in the labeling of the graph noted by the Examiner. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdrawn the foregoing objection to the drawings.

***Objection to the Specification***

The Examiner has objected to the specification "for containing minor errors in sentence structure." In particular, the Examiner is of the opinion that

> on page 14, line 7, "illustrated: pixel" should be changed to -illustrated each representing a--; on page 14, line 26, "using" should be changed to --Using-; on page 15, line 1, "comprise" should be changed to -compnses-; on page 15, lines 10 and 24, "of the remitted" should be changed to -remitted--.

Applicant respectfully submits that the specification has been amended to correct several typographical errors, including the errors noted by the Examiner. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdrawn the foregoing objection to the specification.

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***Benefit of Earlier Filed Application***

With respect to Applicant's right to claim priority to U.S. provisional patent application entitled "Method and Apparatus for Amplifying Pathological Features in Tissues", filed on December 15, 1999, the Examiner is of the opinion that

> [a]n application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet as set forth in 37 CFR 1.78(a)(2) and (a)(5)). Applicant claims the benefit of a U.S. provisional application pursuant to 35 USC 119(e), however applicant does not provide a specific reference to a prior application since the reference given by applicant does not identify the application number of the U.S. provisional Application entitled "Method and Apparatus for Amplifying Pathological Features in Tissues", filed on December 15, 1999. Applicant further claims the benefit of this provisional application on page 3 of the declaration, filed August 30, 2001. The same deficiency noted above is present in this declaration. Thus the present declaration filed August 30, 2001 is objected to and new declaration is required that provides the application serial number of the provisional application that is partially identified in the present declaration. Note that 37 CFR 1.78 (a)(4) states that in order for a nonprovisional application to claim the benefit of one or more prior filed provisional applications, each prior provisional application must name as an inventor at least one inventor named in the later filed nonprovisional application and disclose the named inventor's invention claimed in at least one claim of the later filed nonprovisional application in the manner provided by the first paragraph of 35 U.S.C. 112. In a paper entitled "Letter Regarding Rights of Priority under 35 USC 119(e), a statement is made that the provisional application entitled "Method and Apparatus for Amplifying Pathological Features in Tissues", filed on December 15, 1999 disclosed an embodiment of the invention solely invented by the applicant of the instant application. Further that letter states that the applicant of the instant application was not listed as an inventor in the provisional application and that the filer of the provisional application "has acknowledged that the above-identified Applicant is an inventor of a disclosed embodiment and an appropriate remedy is being sought". In this regard note that 37 CFR 1.48(d) states that "If the name or names of an inventor or inventors were omitted in a provisional application through error without any deceptive intention on the part of the omitted inventor or inventors, the provisional application may be amended to add the name or names of the omitted inventor or inventors. Amendment of the inventorship requires: (1) A request, signed by a party set forth in § 1.33(b), to correct the inventorship that identifies the inventor or inventors being added and states that the inventorship error occurred without deceptive intention on the part of the omitted inventor or inventors; and (2) The processing fee set forth in § 1.17(q). Further 37 CFR 1.48(e) states that "If a person or persons were named as an inventor or inventors in a provisional application through error without any deceptive intention on the part of such person or persons, an amendment may be filed

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> in the provisional application deleting the name or names of the person or persons who were erroneously named. Amendment of the inventorship requires: (1) A request to correct the inventorship that sets forth the desired inventorship change; (2) A statement by the person or persons whose name or names are being deleted that the inventorship error occurred without deceptive intention on the part of such person or persons; (3) The processing fee set forth in § 1.17(q); and (4) If an assignment has been executed by any of the original named inventors, the written consent of the assignee (see § 3.73(b) of this chapter)." Since applicant has not met the requirements set forth in 37 CFR 1.78 (a)(4), 37 CFR 1.48(d) and 37 CFR 1 48(e), applicant may not claim the benefit of a U.S. provisional application pursuant to 35 DSC 119(e). Should applicant file papers which meet the requirements set forth in 37 CFR 1.78 (a)(4), 37 CFR 1,48(d) and 37 CFR 1.48(e), applicant then may claim the benefit of the U.S. provisional application pursuant to 35 USC 119(e).

Applicant respectfully submits that Applicant is entitled to the December 15, 1999 priority date. Accordingly, Applicant will take the appropriate steps to correct the deficiencies of the "Related Applications" section of the specification and the Declaration, Petition and Power of Attorney as noted by the Examiner, prior to the issuance of this application.

***Declaration Under 37 C.F.R. §1.131 Filed on November 25, 2002***

With regard to the Declaration under 37 C.F.R. §1.131 filed on November 25, 2002, the Examiner is of the opinion that the declaration

> is ineffective to overcome the Kauffman references (U.S. Patent Application Publication No. US 2002/0127735 A1 and U.S. Patent Application Publication No. US 20020007122 A1). The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Kauffman references (U.S. Patent Application Publication No. US 2002/0127735 A1 and U.S. Patent Application Publication No. US 20020007122 A1). While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). Applicant presents an article received and accepted by the Journal of Photochemistry and Photobiology as evidence to establish conception of the invention prior to the effective date of the Kauffman references. This article does not describe the step of monitoring the rate of change of light reflection from a tissue sample over time, thereby monitoring the effects of a pathology differentiating agent on the tissue

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> sample, as disclosed by applicant on page 6, lines 29-31 of the instant application. With regard to the declaration filed on December 2, 2002 under 37 CFR 1.131, the evidence submitted is insufficient to establish diligence from a date prior to the date of reduction to practice of the Kauffman reference to either a constructive reduction to practice or an actual reduction to practice. Where conception occurs prior to the date of the reference, but reduction to practice is afterward, it is not enough merely to allege that applicant or patent owner had been diligent. Ex parte Hunter, 1889 C.D. 218, 49 O.G. 733 (Comm'r Pat. 1889). Rather, applicant must show evidence of facts establishing diligence. The record must set forth an explanation or excuse for the inactivity; the USPTO or courts will not speculate on possible explanations for delay or inactivity. See In re Nelson, 420 F.2d 1079, 164 USPQ 458 (CCPA 1970).

Applicant respectfully submits that, contrary to the Examiner's assertions, the Declaration under 37 C.F.R. §1.131 filed on November 25, 2002 is sufficient to show "prior invention," i.e., reduction to practice of the present invention prior to the effective date of U.S. Patent Application Publication No. US 2002/0127735 A1 and U.S. Patent Application Publication No. US 20020007122 A1 (hereinafter "the Kaufman references") for the following reasons.

To begin with, contrary to the Examiner's assertion, the Journal of Photochemistry and Photobiology article submitted by Applicant as evidence to establish prior invention does describe the step of monitoring the rate of change of light reflection from a tissue sample over time, thereby monitoring the effects of a pathology differentiating agent on the tissue sample. Specifically, the article teaches that "[i]n order to improve the sensitivity and specificity of clinical diagnosis we have quantitatively assessed, in vivo, the acetic acid-induced *temporal* and spatial alterations in the light scattering properties of abnormal epithelium by means of a specially developed imaging system." (Emphasis added; See page 154, right column, lines 8-12). The term "temporal" is well known to mean "of or relating to the sequence of time" (see "Merriam Webster's Collegiate Dictionary" (Tenth Edition)). Moreover, at page 155, under the sub-heading "Clinical Measurements" the article provides that "[f]or each member of the groups of patients, the above-described imaging procedure was performed and the *IBSL versus time curves* were automatically calculated and displayed for any selected image area." (Emphasis added). Finally, Figure 2 at page 156 depicts IBSL (intensity of the back scattered light) versus time curves obtained from clinical cases with normal and malignant cervix

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(Figure 2a) and clinical cases with normal and malignant larynx (Figure 2b). In the "Discussion and conclusions" section of the paper, the authors provide that

> [t]he described method introduces a novel approach to the problem of non-destructive tissue diagnostics and staging, by exploiting the diagnostic content of the acetic acid-tissue interaction kinetics. The sensitivity is improved with spectral filtering and with the elimination of surface reflection, which enables the early detection of pre-malignant lesions. ***Acetic acid-tissue interaction has for the first time been quantitatively assessed and the in vivo and in vitro studies, performed during this initial clinical trial, show that differences in the kinetics of the phenomenon are correlated with the malignancy grade. The recorded differences in the IBSL versus time curves and in the derived relaxation time enable unbiased differentiation between malignant and non-malignant epithelial lesions, as well as between malignancies of different grades*** (*Emphasis added*).

In view of the foregoing, it is evident that the Journal of Photochemistry and Photobiology article does describe the step of monitoring the rate of change of light reflection from a tissue sample over time, thereby monitoring the effects of a pathology differentiating agent on the tissue sample.

With respect to the Examiner's assertion that the evidence submitted along with the declaration under 37 C.F.R. §1.131 "is insufficient to establish diligence from a date prior to the date of reduction to practice of the Kauffman reference to either a constructive reduction to practice or an actual reduction to practice," Applicant respectfully submits that the evidence submitted by Applicant is sufficient to show reduction to practice of the present invention prior to the effective date of the Kaufman references. Thus, any inquiry into diligence is not necessary and is irrelevant to this analysis.

Specifically, M.P.E.P. §706.02(b) provides that a rejection based on a 35 U.S C. §102(e) reference may be overcome by

> "[f]iling an affidavit or declaration under 37 CFR 1.131 showing ***prior invention***,

> if the reference is not a U.S. patent (or application in the case of a provisional rejection) claiming the same patentable invention as defined in 37 CFR 1.601(n). See MPEP § 715 for more information on 37 CFR 1.131 affidavits. When the claims of the reference and the application are directed to the same invention or are obvious variants, an affidavit or declaration under 37 CFR 1.131 is not an acceptable method of overcoming the rejection. Under these circumstances, the examiner must determine whether a double patenting rejection or interference is appropriate. (*Emphasis added*).

> There are three ways to show ***prior invention***:
>
> (A) ***reduction to practice of the invention prior to the effective date of the reference***; or (B) conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice; or (C) conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to the filing date of the application (constructive reduction to practice). (*Emphasis added*). M.P.E.P. § 715.07.

With respect to a showing of an actual reduction to practice, M.P.E.P. §715.07 provides that "[i]n general, proof of actual reduction to practice requires a showing that the apparatus actually existed and worked for its intended purpose." Moreover, M.P.E.P. §2138.05 provides that "[i]n an interference proceeding, a party seeking to establish an actual reduction to practice must satisfy a two-prong test: (1) the party constructed an embodiment or performed a process that met every element of the interference count, and (2) the embodiment or process operated for its intended purpose." *Eaton v. Evans*, 204 F.3d 1094, 1097, 53 USPQ2d 1696, 1698 (Fed. Cir. 2000). M.P.E.P. §2138.05 further provides that "***[a] process is reduced to practice when it is successfully performed.***" (*Emphasis added*). Corona *v. Donan*, 273 U.S. 692, 1928 C.D. 252 (1928); *Fitzgerald v. Arbib*, 268 F.2d 763, 765-66, 122 USPQ 530, 531-32 (CCPA 1959). In the present case, it is clear from the evidence submitted by Applicant (the *Journal of Photochemistry and Photobiology* article) that ***the claimed method was successfully performed prior to December 15, 1999***, the effective 35 U.S.C. §102(e) date of the Kaufman references. As evidenced by the *Journal of Photochemistry and Photobiology* article, Applicant had applied a pathology

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differentiating agent on a tissue sample, wherein the pathology differentiating agent chemically interacts with the tissue sample and alters its optical characteristics (see, for example, page 155, right column, lines 5-10 and page and page 154, right column, lines 8-12); and had monitored the rate of change of light reflection from the tissue sample over time (see, for example, Figure 2), thereby monitoring the effects of a pathology differentiating agent on a tissue sample (see, for example, page 155, left column, the paragraph that starts "Fig. 2(a) illustrates"). Moreover, Applicant had contacted a tissue in a subject with a pathology differentiating agent, wherein the pathology differentiating agent chemically interacts with the tissue sample and alters its optical characteristics (see, for example, page 155, right column, lines 5-10 and page and page 154, right column, lines 8-12); had exposed the tissue in the subject to optical radiation (see, for example, page 154, left column, lines 33-36); and had monitored the intensity of light emitted from the tissue over time (see, for example, Figure 2), thereby diagnosing a tissue abnormality in a subject ( see, for example, page 157, right column, the paragraph that starts with "The limitations of conventional techniques").

In view of all of the foregoing, Applicant respectfully submits that the Declaration under 37 C.F.R. §1.131 filed on November 25, 2002 is sufficient to show "prior invention," *i.e.*, reduction to practice of the present invention prior to the effective date of the Kaufman references. Thus, if the Examiner believes that the Kaufman references are appropriate references under 35 U.S.C. §102(e) (rather than patent applications with which an interference should be declared), the foregoing declaration is sufficient to overcome the Kaufman references.

***Rejection of Claims 1-5 Under 35 U.S.C. §102(e)***

The Examiner has rejected claims 1-5 under 35 U.S.C. §102(e) as being anticipated by Kaufman *et al.* (U.S. Publication No. US 2002/0127735 A1). The Examiner relies on Kaufman *et al.* for disclosing "a method for monitoring the effects of a pathology differentiating agent on a tissue sample, comprising: applying a pathology differentiating agent (see page 1, lines 3-6 of

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paragraph [0006]), wherein said pathology differentiating agent chemically interacts with said tissue sample and alters its optical characteristics; and monitoring the rate of change of light reflection from said tissue sample over time (see page 6, paragraph [0072] and page 11, paragraph [0114]), thereby monitoring the effects of a pathology agent on a tissue sample."

Applicant respectfully traverses the foregoing rejection on the grounds that the Kaufman *et al.* reference is not available as a 35 U.S.C. §102(e) prior art reference against Applicant's invention. As demonstrated above, the declaration under 37 CFR §1.131 filed on November 25, 2002 is sufficient to show that Applicant had completed the invention as described and claimed in the instant patent application in this country, a NAFTA country, or a WTO country, prior to ***December 15, 1999***. Kaufman *et al.* has an effective 35 U.S.C. §102(e) date of ***December 15, 1999***. Accordingly, Applicant respectfully submits that the invention disclosed in the present patent application was reduced to practice by the inventor prior to the effective date of Kaufman *et al.* As such, the Kaufman *et al.* reference is not available as prior art against the present invention under 35 U.S.C. §102(e) and, accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

***Rejection of Claims 6, 7, 9-13 and 16 Under 35 U.S.C. §102(e)***

The Examiner has rejected claims 6, 7, 9-13 and 16 under 35 U.S.C. §102(e) as being anticipated by Richards-Kortum *et al.* The Examiner relies on Richards-Kortum *et al.* for disclosing

> a method for the *in vivo* diagnosis of a tissue abnormality in a subject comprising contacting a tissue in a subject with a pathology differentiating agent (see col 2, lines 44-46), wherein said pathology differentiating agent chemically interacts with said tissue sample and alters its optical characteristics (see col. 2, lines 47-48), exposing said tissue in said subject to optical radiation (see col. 1, lines 47-48), and monitoring the intensity of light emitted from said tissue over time (see col. 1, lines 48-53 and 60-61 and col. 2, lines 49-50), thereby diagnosing a tissue abnormality in a subject (see col. 1, lines 62-67). Richards-Kortum uses acetic acid as the pathology differentiating agent (see col. 2, lines 41-43). The high resolution imaging disclosed by Richards-Kortum can be used to obtain near real-time reflected light images of the tissue being examined. Since Richards-Kortum discloses that multiple images are being obtained,

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the monitoring of the intensity of light emitted from the tissue in Richards-Kortum is being done "over time".

Applicant respectfully traverses the forgoing rejection for the following reasons. Claim 1 and claims depending therefrom, are directed to a method for monitoring the effects of a pathology differentiating agent on a tissue sample by applying a pathology differentiating agent on a tissue sample, wherein the pathology differentiating agent chemically interacts with the tissue sample and alters its optical characteristics; and ***monitoring the rate of change of light reflection from the tissue sample over time***, thereby monitoring the effects of a pathology differentiating agent on a tissue sample. Claim 6 and claims depending therefrom, are directed to a method for the *in vivo* diagnosis of a tissue abnormality in a subject, by contacting a tissue in a subject with a pathology differentiating agent, wherein the pathology differentiating agent chemically interacts with the tissue sample and alters its optical characteristics; exposing the tissue in the subject to optical radiation; and ***monitoring the intensity of light emitted from the tissue over time***, thereby diagnosing a tissue abnormality in a subject.

For a prior art reference to anticipate in terms of 35 U.S.C. § 102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicant respectfully submits that Richards-Kortum *et al* do not teach or suggest the methods of claims 1 and 6 and claims depending therefrom. Richards-Kortum *et al.* disclose a method which is based on the ***static imaging*** of a tissue sample. In contrast, the claimed invention is directed to methods which involve ***monitoring the intensity of light emitted from the tissue over time***, *i.e.*, monitoring the kinetics of the effects of acetic acid on a tissue sample. Nowhere do Richards-Kortum *et al.* teach or suggest monitoring the intensity of light emitted from the tissue over time.

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In view of the foregoing, it is evident that Richards-Kortum *et al.* fail to teach or suggest each and every element of claims 1 and 6, and claims depending therefrom. Accordingly, Applicant respectfully requests that this section 102(e) rejection, be reconsidered and withdrawn.

***Rejection of Claim 8 Under 35 U.S.C. §103(a)***

The Examiner has rejected claim 8 under 35 U.S.C. §103(a) as being unpatentable over Richards-Kortum *et al.* in view of Zavislan. The Examiner is of the opinion that "[t]o utilize polarized optical radiation in the method of Richards-Kortum as suggested by Zavislan (at col. 2, lines 18-20) would have been obvious since Zavislan states this technique results in a reduction in the amount of surface reflection."

Applicant respectfully traverses the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following arguments is respectfully requested.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F 2d 281, 227 USPQ 657 (Fed. Cir. 1985).

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Applicant respectfully submits that, as indicated above, Richards-Kortum *et al.* fail to teach or suggest methods which involve ***monitoring the intensity of light emitted from the tissue over time,*** *i.e.*, monitoring the kinetics of the effects of acetic acid on a tissue sample. Moreover, Richards-Kortum *et al.* teach away from the claimed invention in that they teach that their method, which is based on the ***static imaging*** of cells in a tissue sample, has been successful. Thus, an ordinarily skilled artisan reading Richards-Kortum *et al.* would not have been motivated to look for other methods of imaging tissue *in vivo*, nor would the ordinarily skilled artisan have a reasonable expectation of success in arriving at Applicant's invention.

Furthermore, Richards-Kortum *et al.* constitutes "non-analogous prior art." The methods of Richards-Kortum *et al.* are based on Confocal Imaging of tissue cells and nuclei. Confocal imaging instrumentation includes laser light (usually infrared) to illuminate very small object areas determined by the "confocal spot." Confocal imaging-based methods require spatial scanning to obtain 3-D images of very small areas comparable with the size of the cells. Therefore, confocal imaging can provide images of tissue areas of very limited size (about 100μm) (see the figures of Richards-Kortum *et al.*). Due to this fact, the examination of the entire surface of the tissue requires millions of small sites to be examined, which is practically unattainable. This is a serious restricting factor for *in vivo* clinical implementation of the Richards-Kortum *et al.* method. In contrast, the method described in the present application employs conventional (non- confocal) 2-D macroscopic imaging of large surfaces of tissues (approximately 1-2 cm). The method enables the assessment of the acetowhitening kinetics simultaneously in any spatial point of the entire surface of the tissue and, thus, may be clinically implemented very easily.

The secondary reference relied on by the Examiner, namely Zavislan does not make up for the deficiencies in the primary reference. Specifically, Zavislan is directed to "imaging systems which enhance image quality by reducing noise which reduces contrast in images especially images obtained from turbid media, such as encountered in biological specimens, and especially dermatological tissue wherein keratin is present." (See column 1, lines 12-19). Nowhere does

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Zavislan teach or suggest methods which involve ***monitoring the intensity of light emitted from the tissue over time***, *i.e.*, monitoring the kinetics of the effects of acetic acid on a tissue sample, as required by Applicant's pending claims.

For the foregoing reasons, the combination of Richards-Kortum et al. and Zavislan does not lead to the claimed invention since the cited references simply do not teach or suggest all of the claim limitations, and cannot lead to the claimed invention. Accordingly, rejection of the pending claims under 35 U.S.C. §103 is believed to be improper and Applicant respectfully requests that it be reconsidered and withdrawn.

***Rejection of Claim 14 and 15 Under 35 U.S.C. §103(a)***

The Examiner has rejected claims 14 and 15 under 35 U.S.C. §103(a) as being unpatentable over Richards-Kortum *et al.* The Examiner is of the opinion that "[t]he particular type of tissue to which the tissue may be exposed (ear, esophagus, etc.) could have been selected in an obvious manner since Richards-Kortum et al state that their method applies to multiple tissue types and should be useful for improving contrast in a variety of organ sites (see col. 4, lines 36-41)."

Applicant respectfully traverses the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following arguments is respectfully requested.

As indicated above, not only do Richards-Kortum *et al.* fail to teach or suggest methods which involve ***monitoring the intensity of light emitted from the tissue over time***, *i.e.*, monitoring the kinetics of the effects of acetic acid on a tissue sample, as required by Applicant's pending claims, but they also teach away from the claimed invention by teaching that other methods of imaging tissue, *i.e.*, methods that are based on the ***static imaging*** of cells in a tissue sample, have been successful. Thus, an ordinarily skilled artisan reading Richards-Kortum *et al.* would not have been motivated to look for other methods of imaging tissue *in vivo*, nor would the ordinarily skilled artisan have a reasonable expectation of success in arriving at Applicant's invention.

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For the foregoing reasons, the Richards-Kortum *et al.* reference does not lead to the claimed invention since this reference simply does not teach or suggest all of the claim limitations, and cannot lead to the claimed invention. Accordingly, this rejection of claims 14 and 15 under 35 U.S.C. §103 is believed to be improper and Applicant respectfully requests that it be reconsidered and withdrawn.

***Declaration Under 37 C.F.R. §1.132 Filed on November 25, 2002***

With respect to the declaration under 37 C.F.R. §1.132 filed on November 25, 2002, the Examiner is of the opinion that

> 37 CFR 1.132 states that "When any claim of an application or a patent under reexamination is rejected or objected to, any evidence submitted to traverse the rejection or objection on a basis not otherwise provided for must be by way of an oath or declaration under this section.". The declaration filed by applicant is not directed to the traverse of a rejection made in the last mailed Office action (paper no. 6). Rather applicant states that he is the co-author of a paper and that the other co-authors are not co-inventors of the subject matter described and claimed in the instant application. Thus it would appear that the declaration was not filed properly under 37 CFR 1.132. Notwithstanding the above, it is noted that a declaration filed pursuant to 37 CFR 1.132 must be supported by evidence. Applicant offers only opinion testimony on the ultimate legal conclusion at issue (viz. that the co-authors are not co-inventors of the subject matter disclosed in the instant application). Such opinion as to a legal conclusion is not entitled to any weight.

Applicant respectfully submits that, contrary to the Examiner's assertions, the declaration under 37 C.F.R. §1.132 filed on November 25, 2002 does not only offer opinion testimony on the ultimate legal conclusion at issue. In contrast, the declaration offers ***statements of fact*** describing the contribution of each of the authors to the publication, *i.e* , that: (a) George C. Themelis was a graduate student in Dr. Balas' (the inventor's) lab who performed technical aspects described in the publication under Dr. Balas' direction and supervision, (b) Emmanuel P. Prokopakis and Irene Orfanudaki were medical residents who performed technical aspects described in the publication at the request and under the direction and supervision of Dr. Balas; and (c) Eugenios

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Koumantakis and Emmanuel S. Helidonis are directors at the clinics were the clinical work described in the publication was performed and did not otherwise contribute to the work described in this publication. Nonetheless, as correctly pointed out by the Examiner, since the Declaration is not necessary to overcome any rejection this issue is moot.

***U.S. Publication Number US 2002/0127735 A1 and U.S. Publication Number US 20020007122 A1***

With regard to U.S. Publication Number US 2002/0127735 A1 and U.S. Publication Number US 20020007122 A1, the Examiner is of the opinion that

> Applicant's arguments filed December 6, 2002 and December 17, 2002 have been fully considered. Applicant states that "the claims presented herein essentially correspond to the claims of U.S. Publication Number US 2002/0127735 A1 and U.S. Patent Application Publication Number US 20020007122 A1.". The examiner disagrees with this conclusion since claim 1 of U.S. Publication Number US 2002/0127735 A1 recites "dispensing a plurality of chemical agents on a tissue, wherein the chemical agents interact to alter an optical signal produced by the tissue". Applicant's claim 1 merely recites applying a pathology differentiating agent on a tissue sample, wherein said pathology differentiating agent chemically interacts with said tissue sample and alters its optical characteristics". Applicant's claim 1 says nothing about dispensing a plurality of chemical agents on a tissue *wherein the chemical agents interact* (emphasis added) as claimed by U.S. Publication Number US 2002/0127735 A1. Indeed applicant lacks disclosure to support such a claim. The same comments apply to U.S. Patent Application Publication Number US 20020007122 A1.

As stated above, the Examiner takes the position that claim 1 of U.S. Publication Number US 2002/0127735 A1 which recites "dispensing a plurality of chemical agents on a tissue, wherein the chemical agents interact to alter an optical signal produced by the tissue" is different from Applicant's claim 1 which recites "applying a pathology differentiating agent on a tissue sample, wherein said pathology differentiating agent chemically interacts with said tissue sample and alters its optical characteristics." Applicant respectfully disagrees with the Examiner for the following reasons. As indicated by a mere comparison of the claims (facilitated by the table set forth below), claim 1 of the

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present application is directed to the "same patentable invention" as claim 1 of U.S Publication Number US 2002/0127735 A1.

| Claim 1 of U.S. Publication Number US 2002/0127735 A1 | Claim 1 of the Present Application |
|---|---|
| dispensing | applying |
| a plurality of chemical agents | a pathology differentiating agent |
| on a tissue | on a tissue sample |
| wherein the chemical agents interact to alter an optical signal produced by the tissue | wherein said pathology differentiating agent chemically interacts with said tissue sample and alters its optical characteristics |

As indicated in the Supplemental Amendment filed on December 17, 2002, it is a well established principle of patent law that "an indefinite article 'a' or 'an' in patent parlance carries the meaning of 'one or more' in open-ended claims containing the transitional phrase 'comprising.'" *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 55 USPQ2d 1835 (Fed. Cir. 2000); *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 977, 52 USPQ2d 1109, 1112 (Fed Cir 1999); *AbTox, Inc. v. Exitron Corp.*, 122 F3d 1019, 1023, 43 USPQ2d 1545, 1548 (Fed. Cir. 1997); *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1575-76, 28 USPQ2d 1333, 1336 (Fed. Cir. 1993); *see also* Robert C. Faber, *Landis on Mechanics of Patent Claim Drafting* 531 (3d ed. 1990). Thus, in the present case, Applicant's claim 1 covers the application of one or more pathology differentiating agents to a tissue sample.

Moreover, contrary to the Examiner's assertion, Applicant's claim 1 does expressly recite that the pathology differentiating agent (which as defined is the same as the chemical agent of U.S. Publication Number US 2002/0127735 A1) interacts with the tissue. Support for this claim language may be found throughout Applicant's specification. For example, support may be found at page 7,

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lines 17-21, where Applicant teaches that "[i]n one embodiment, the tissue area of interest is illuminated with a broad band optical radiation and ***contacted with a pathology differentiating agent, e.g., an agent or a combination of agents which interact with pathologic tissue areas*** characterized by an altered biochemical composition and/or cellular functionality and provoke a transient alteration in the characteristics of the light that is re-emitted from the tissue." (*Emphasis added*).

If the Examiner is taking the position that claim 1 of U.S. Publication Number US 2002/0127735 A1 requires that the chemical agents interact among themselves to alter an optical signal produced by the tissue, Applicant respectfully submits that this interpretation of the claim is inconsistent with the express teachings in U.S. Publication Number US 2002/0127735 A1. Specifically, this patent application (as well as the 20020007122 A1 application) teach that

> [a]ccording to the invention, changes in the spectral properties of tissues upon exposure to chemical agents are characteristic of the physiological state of the tissue. In particular, ***the invention relates to changes in spectral properties of a sample in response to chemical treatment. ... When exposed to a chemical agent, such as a contrast agent, the spectral properties of the tissue are changed by the interaction of the agent with endogenous molecules in the tissue***. (*Emphasis added*; see paragraph [0006] of both the '735 and the '122 applications).

In view of the foregoing, it is evident that claim 1 of both the '735 and the '122 applications requires that the chemical agents ***interact with the tissue*** to alter an optical signal produced by the tissue.

Even assuming *arguendo* that claim 1 of the present application is not the same (as in 35 U.S.C. §102) as claim 1 of the '122 and the' 735 applications, which Applicant unequivocally disputes, Applicant respectfully submits that, with respect to an interference,

> [i]nvention "A" is the same patentable invention as an invention "B" when invention "A" is the same as (35 U.S.C. 102) or is obvious (35 U.S.C. 103) in view of invention "B" assuming invention "B" is prior art with respect to

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> invention "A". Invention "A" is a separate patentable invention with respect to invention "B" when invention "A" is new (35 U.S.C. 102) and non-obvious (35 U.S.C. 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A". See 37 C.F.R. §1.601(n)

In view of all of the foregoing, it is evident that claim 1 of the '122 and the' 735 applications is, at least, obvious over claim 1 of the present application.

Finally, if despite the foregoing arguments the Examiner insists on maintaining the position that the pending claims are not directed to the "same patentable invention" as the claims in U.S. Publication Numbers US 2002/0127735 A1 and US 20020007122 A1, Applicant invites the Examiner to indicate the pending claims as allowable and allow them to proceed to issuance

**SUMMARY**

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested.

If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

Maria Laccotripe Zacharakis, Ph.D
Limited Recognition Under 37 C.F.R. §10.9(b)
Attorney for Applicant

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
(617) 227-7400
Dated: January 30, 2003

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Please replace the paragraph beginning at page 14, line 7 with the following re-written paragraph:

--In Figure 1, two curves are illustrated: each representing a pixel value in position xy (Pvxy), versus time t. The curve ATC corresponds to an area where agent administration provoked alterations (AT) in the tissue's optical characteristics. The curve ~~(NATC)~~ NAT corresponds to an area where no alteration took place (NAT).

Please replace the paragraph beginning at page 14, line 15 with the following re-written paragraph:

-- The calculation of these parameters (P) in every spatial point of the area under analysis, allows the calculation of the image or images of the kinetics of the phenomenon (KI), with pixel values that are correlated with these parameters. These values can be represented with a scale of pseudocolors (**Pmin, Pmax**), the spatial distribution of which allows for immediate optical evaluation of the intensity and extent of the provoked alterations. Depending on the correlation degree between the intensity and the extent of the provoked alterations with the pathology and the stage of the tissue lesion, the measured quantitative data and the derived parameters would allow the mapping, the characterization and the border-lining of the lesion. The pseudocolor image of the phenomenon's kinetics (KI), which expresses the spatial distribution of one or more parameters, can be overimposed (after being calculated) on the tissue image, which is displayed in real-time on the monitor. ~~The using~~ Using the overimposed image as a guide, facilitates substantially the determination of the lesion's boundaries, for successful surgical removal of the entire lesion, or for locating suspicious areas in order to obtain a biopsy sample(s). Furthermore, based on the correlation of the phenomenon's kinetics with the pathology of the tissue, the measured quantitative data and the parameters that derive from them, can constitute quantitative clinical indices for the *in vivo* staging of the lesion or of sub-areas of the latter.--

Please replace the paragraph beginning at page 14, line 33 with the following re-written paragraph:

--In some cases it is necessary to capture the kinetics of the phenomenon in more than one spectral band. This can serve in the in vivo determination of illumination and/or imaging spectral

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bands at which the maximum diagnostic signal is obtained. Furthermore, the simultaneous imaging in more than one spectral bands can assist in minimizing the contribution of the unwanted endogenous scattering, fluorescence and reflection of the tissue, to the optical signal captured by the detector. The captured optical signal ~~comprise~~ comprises the optical signal generated by the marker-tissue interaction and the light emitted from the endogenous components of the tissue. In many cases the recorded response of the components of the tissue constitute noise, since it occludes the generated optical signal, which caries the diagnostic information. Therefore, separation of these signals, based on their particular spectral characteristics, will result in the maximization of the signal-to-noise ratio and consequently in the improvement of the obtained diagnostic information.

Please replace the paragraph beginning at page 15, line 8 with the following re-written paragraph:

--Figure 2, illustrates a method for capturing in two spectral bands simultaneously and in any spatial point of the area under analysis, the kinetics of the alterations in the characteristics of the light remitted from the tissue ~~light~~, before and the after the administration of the contrast enhancing agent. The remitted from the tissue light, is collected and focused by the optical imaging module (L) and passes through a beam splitting (BSP) optical element. Thus, two identical images of the tissue (T) are generated, which can be captured by two detectors (D1, D2). In front of the detector, appropriate optical filters (Ofλ1), (Ofλ2) can be placed, so that images with different spectral characteristics are captured. Besides beam splitters, optical filters, dichroic mirrors etc, can also be used for splitting the image of the object. The detectors (D1), (D2) are synchronized so that they capture simultaneously the corresponding spectral images of the tissue (Tiλ1), (Tiλ2) and in successive time-intervals, which are stored in the computer's data storage means. Generalizing, multiple spectral images can be captured simultaneously by combining multiple splitting elements, filters and sources.--

Please replace the paragraph beginning at page 15, line 22 with the following re-written paragraph:

--Figure 3 illustrates another method for capturing in different spectral bands simultaneously and in any spatial point of the area under analysis, the kinetics of the alterations in the characteristics of the light remitted from the tissue ~~light~~, before and the after the administration of the contrast enhancing agent With the aid of a special prism (MIP) and imaging optics, it is possible to form multiple copies of the same image onto the surface of the

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same detector (D). Various optical filters (OFλ1),(OFλ2),(OFλ3),(OFλ4), can be interposed along the length of the optical path of the rays that form the copies of the object's image, so that the captured multiple images correspond to different spectral areas.--

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